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REVIEW ARTICLE

A four-domain framework for secondary immunodeficiency after CAR T-cell and T-cell-engaging antibody therapy

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Abstract

Chimeric antigen receptor (CAR) T-cell therapies and T-cell-engaging antibodies have transformed the treatment of hematologic malignancies but can induce prolonged, overlapping, and dynamically evolving immune deficits that are not adequately captured by hypogammaglobulinemia alone. Infection susceptibility reflects the interplay among the underlying disease and prior treatment, the immune-effector modality and therapeutic target, the predominant immune-deficit phenotype, and its evolution over time. We therefore propose a four-domain framework—Disease substrate, Drug and target, Deficit profile, and Dynamics—as a pragmatic structure for longitudinal characterization of secondary immunodeficiency after CAR T-cell and T-cell-engaging antibody therapy. The framework integrates myeloid, humoral, cellular, combined, and mucosal or epithelial barrier deficits with treatment-specific exposures and patterns of immune recovery, linking them to phenotype- and phase-adapted monitoring and prevention. We synthesize evidence on infection epidemiology, immune reconstitution, vaccination, antimicrobial prophylaxis, and immunoglobulin replacement while distinguishing established recommendations from practices supported mainly by observational data or expert consensus. A dynamic, phenotype-guided approach may improve targeting of preventive interventions while limiting avoidable prophylactic exposure. Priority research needs include standardized immune and infection end points, prospective longitudinal immune phenotyping, externally validated dynamic risk models, and comparative-effectiveness studies of immunoglobulin replacement, response-adapted extension of dosing intervals for T-cell-engaging antibodies, and antimicrobial prophylaxis.

Keywords: Secondary immunodeficiency; CAR T-cell therapy; T-cell-engaging antibodies; Bispecific antibodies; Infection; Immune reconstitution; Immunoglobulin replacement; Immune monitoring

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1. Introduction

Cellular and T-cell-redirecting immunotherapies have broadened therapeutic options and, in several disease settings, improved clinical outcomes. Their effects on host defense are multifactorial, reflecting the underlying malignancy and prior treatment as well as preparative regimens, on-target effects on nonmalignant immune-cell compartments, treatment-associated toxicities, and the interventions used to manage them. Lymphodepleting chemotherapy, prolonged or biphasic cytopenias, depletion of

normal B cells or plasma cells, hypogammaglobulinemia, delayed CD4-positive T-cell reconstitution, mucosal injury, prior hematopoietic cell transplantation, and toxicity-directed immunosuppression—particularly corticosteroid exposure—may collectively generate overlapping and dynamically evolving immune deficits.[1-5] CD19-directed CAR T-cell therapies are established treatment options for selected patients with B-cell acute lymphoblastic leukemia and B-cell lymphomas.[1] In heavily pretreated multiple myeloma, B-cell maturation antigen (BCMA)-directed CAR T-cell therapies and BCMA- or G protein-coupled receptor class C group 5 member D (GPRC5D)-directed bispecific antibodies have achieved high response rates in clinical trials.[6-10]

The infectious phenotype is heterogeneous and evolves over time. In the early post-infusion period, bacterial infections are frequently observed in the context of neutropenia, mucosal barrier injury, central venous access, hospitalization, and acute immune-effector-cell toxicities and their management. At later time points, respiratory viral infections and bacterial respiratory tract infections may become relatively more prominent. Less common events—including herpesvirus reactivation, *Pneumocystis jirovecii* pneumonia (PJP), invasive fungal disease, and other opportunistic infections—are reported particularly among patients with persistent or overlapping immune deficits, such as prolonged lymphopenia, B-cell aplasia, hypogammaglobulinemia, prolonged neutropenia, or additional immunosuppressive exposure.[1,11] With repeated or continuous bispecific-antibody therapy, infection rates may remain elevated and the cumulative burden of infection may increase over time, particularly with BCMA-directed agents. Persistent depletion of normal plasma cells and sustained impairment of humoral immunity are likely important contributors, although disease-related and other treatment-related factors remain relevant.[2,8,10,12–18]

The evidence base informing current practice is heterogeneous, comprising prospective trials[6-10], retrospective and real-world cohorts[5,12–14,19,20], systematic reviews and meta-analyses[15,17,18], and expert recommendations or consensus statements.[1–4,11,16] Existing guidance already considers multiple patient-, disease-, treatment-, and immune-related risk factors. The remaining practical gap is therefore not recognition that infection susceptibility is multifactorial, but the absence of a consistent cross-modality structure for repeatedly organizing and updating these factors as treatment exposure, immune deficits, infections, and recovery change over time. In clinical practice and research, interpretation may still become anchored to isolated markers such as total IgG or to fixed post-treatment intervals, which can obscure discordance between a laboratory value, the predominant deficit phenotype, and the current treatment state. We therefore propose a multidimensional framework that conceptualizes infection susceptibility as a time-indexed phenotype and provides a common structure for longitudinal clinical assessment, research standardization, and the future development of dynamic risk models.

2. Literature approach

This state-of-the-art review was informed by structured searches of PubMed/MEDLINE and by reference-list screening of relevant society guidance, consensus statements, systematic reviews and meta-analyses, pivotal clinical trials, and recent real-world cohorts. Search concepts combined terms relating to CAR T cells; bispecific and other T-cell-engaging antibodies; CD19, CD20, BCMA, and GPRC5D; multiple myeloma and lymphoma; infection; secondary immunodeficiency; hypogammaglobulinemia; immune reconstitution; antimicrobial prophylaxis; vaccination; and immunoglobulin replacement. Priority was given to peer-reviewed clinical evidence directly informing infection epidemiology, immune dysfunction, monitoring, or prevention, while recent systematic reviews and meta-analyses were used to contextualize heterogeneous primary data. The final search update was conducted on August 26, 2026. Because the most detailed evidence on sustained immune dysfunction during T-cell-engaging antibody therapy currently derives from multiple myeloma—particularly BCMA-directed therapy, with more limited but clinically relevant evidence for GPRC5D-directed agents—these settings receive greater emphasis. Evidence from CD19-directed CAR T-cell therapy and CD20×CD3 bispecific-antibody therapy in B-cell malignancies is incorporated where relevant. The review was designed as an integrative conceptual synthesis rather than an exhaustive or quantitative synthesis. Accordingly, no formal risk-of-bias assessment, certainty-of-evidence grading, or meta-analysis was performed. A reproducible search strategy is provided in the Supplementary Methods (see Appendix).

3. Why modern immune therapies generate distinct secondary immunodeficiency phenotypes

Secondary immunodeficiency after immune-effector therapy reflects multiple, interacting layers of vulnerability. The underlying malignancy may compromise host defense before treatment begins: multiple myeloma is commonly associated with immunoparesis, whereas B-cell malignancies may disrupt normal B-cell number, function, or both. In addition, patients referred for CAR T-cell or

bispecific-antibody therapy are often heavily pretreated, with prior exposures that may include anti-CD20 or anti-CD38 antibodies, proteasome inhibitors, immunomodulatory drugs, autologous or allogeneic hematopoietic cell transplantation, corticosteroids, and cytotoxic chemotherapy. Baseline infection susceptibility is therefore highly heterogeneous and frequently predates the index immune-effector therapy.[1-5]

The therapeutic target superimposes a characteristic immunologic signature. CD19-directed therapy depletes CD19-expressing nonmalignant B cells and can result in prolonged B-cell aplasia.[1,5,11] BCMA-directed therapy can deplete normal plasma cells and cause marked, sometimes prolonged, reductions in polyclonal immunoglobulins.[2,12–13,15–16,19,20] GPRC5D-directed therapy has a distinct on-target toxicity profile, including dysgeusia, xerostomia, and other oral or epithelial effects.[9,21] Infections nevertheless remain clinically relevant during GPRC5D-directed therapy, with risk shaped by prior treatment burden, baseline immune dysfunction, treatment duration, combination therapy, and other concomitant immunosuppressive exposures.[9,14,17,18]

The pattern and duration of therapeutic exposure provide an additional source of heterogeneity. Whereas CAR T-cell products are administered as a single infusion, bispecific antibodies are generally administered repeatedly or continuously. Ongoing treatment may therefore sustain pharmacologic target engagement and treatment-related immune perturbation over months or longer.[2,8–10,12,14–16] This distinction concerns the mode of treatment delivery and does not imply that the biological effects of CAR T-cell therapy are necessarily short-lived. Treatment-associated inflammation, acute toxicities, and their management further modify infection susceptibility. Management of severe or refractory cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) may require corticosteroids, thereby adding a potentially important but variable source of immunosuppression.[1,22] Prolonged or biphasic cytopenias after CAR T-cell therapy may extend periods of vulnerability beyond resolution of acute toxicities.[1] Taken together, these overlapping mechanisms support longitudinal, phenotype-based assessment rather than risk attribution based on therapeutic class or target alone.

4. The 4D-SID framework

The four-domain framework for secondary immunodeficiency (4D-SID framework) organizes clinically relevant information into four interrelated domains: Disease substrate, Drug and target, Deficit profile, and Dynamics (Figure 1). It is intended as a descriptive framework for longitudinal characterization of the immune state rather than as a prescriptive management algorithm or a weighted, validated risk model. Accordingly, it does not supersede product labeling, institutional protocols, or guideline-based recommendations. Its purpose is to provide a common structure for clinical assessment, communication, and research, thereby clarifying why patients receiving the same therapy may have different infection-risk profiles and why an individual patient's risk may evolve over time. Its proposed added value is the consistent four-domain organization and longitudinal updating of already recognized risk factors, rather than the claim that multifactorial infection susceptibility is newly identified. The domains and their intended clinical role are summarized in Table 1.

The four domains were selected by the author through iterative conceptual grouping of recurrent variables identified in the literature synthesis, including treatment-specific guidance and consensus statements, infection and immune-reconstitution cohorts, and existing risk-stratification work.[1–5,11–16,23,24] This was an author-derived organizational step, not a Delphi process, formal consensus exercise, data-driven feature-selection procedure, or clinical validation study. The grouping was refined to distinguish relatively pre-existing vulnerability (Disease substrate), current therapeutic mechanism and exposure (Drug and target), the observed immune-deficit phenotype (Deficit profile), and longitudinal change in exposure or immune state (Dynamics).

Disease substrate encompasses malignancy-associated immune dysfunction; prior treatment and hematopoietic cell transplantation; baseline infection history and burden; comorbidity; organ dysfunction and physiologic reserve; nutritional and performance status; known colonization; and prior antimicrobial exposure. Drug and target encompasses the therapeutic modality and antigen target; lymphodepletion and bridging therapy; combination partners; dose, dosing interval, and treatment intensity; the treatment-delivery pattern, including single-infusion cellular therapy versus repeated or continuous antibody dosing; and immunosuppressive treatment used to manage therapy-related toxicities. Deficit profile describes the predominant clinically relevant immune deficit, or combination of deficits, including severe or prolonged neutropenia and other clinically relevant myeloid abnormalities; quantitative or functional humoral deficiency; CD4-positive T-cell deficiency or broader cellular immune dysfunction; combined immunodeficiency; and mucosal or epithelial barrier vulnerability. Dynamics captures how these features evolve over time, including time since infusion or treatment

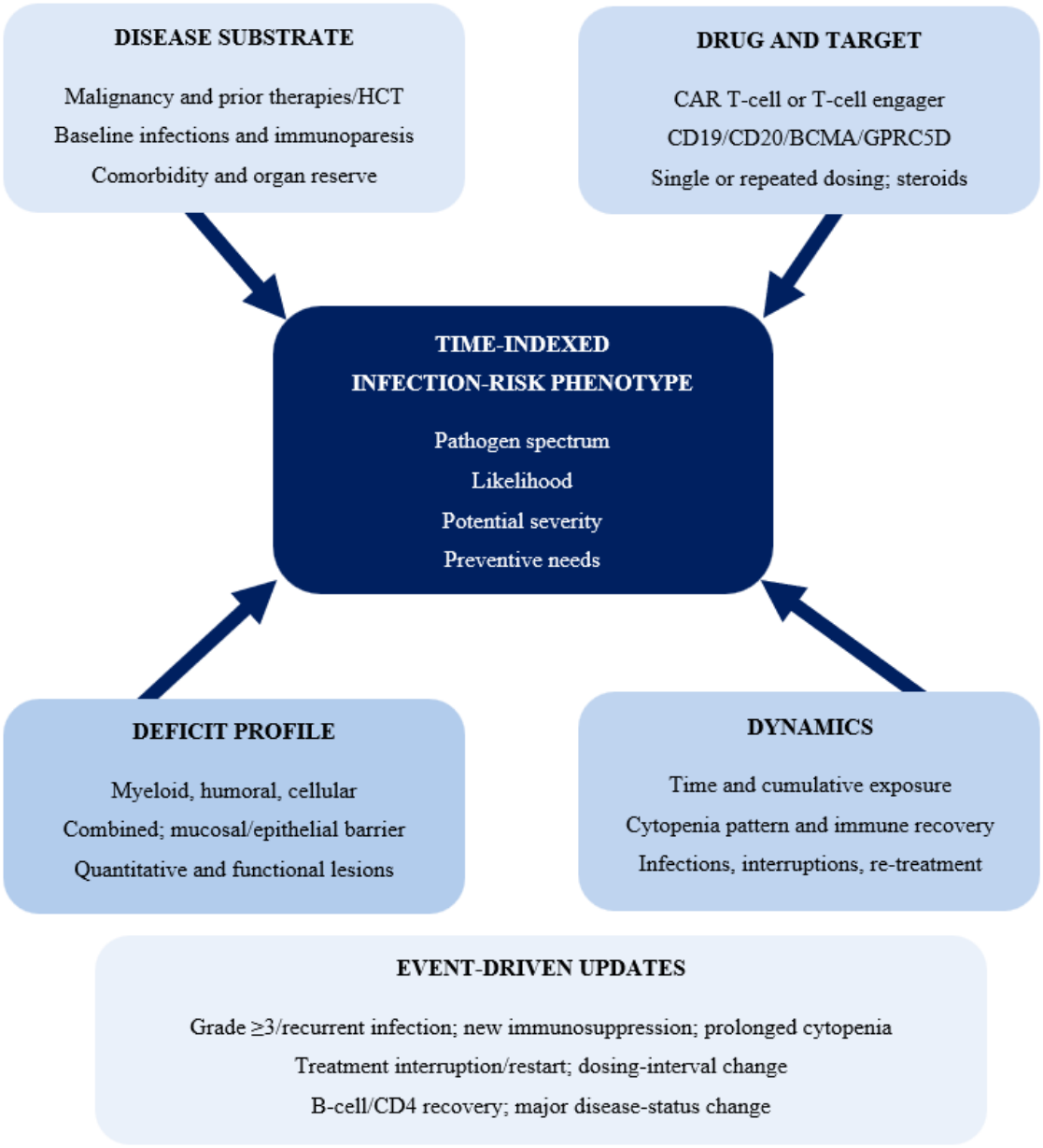


Figure 1. The 4D-SID framework. Four interacting domains—Disease substrate, Drug and target, Deficit profile, and Dynamics —define a time-indexed infection-risk phenotype. The framework is descriptive and is not a weighted or validated prediction model.
Abbreviations: BCMA: B-cell maturation antigen; CAR T: Chimeric antigen receptor T cell; CD4: Cluster of differentiation 4; GPRC5D: G protein-coupled receptor class C group 5 member D; HCT: Hematopoietic cell transplantation.

initiation; treatment duration and cumulative exposure; the onset, persistence, recurrence, and recovery of immune deficits; treatment interruption or restart; additional immunosuppressive exposure; clinically significant infection events; and changes in immune status following infection or documented immune reconstitution.

The four domains are intentionally interrelated rather than statistically independent. For example, the current agent, target, dose, and dosing interval are captured under Drug and target, whereas changes in interval, cumulative exposure, interruption or restart, and recovery over time are captured under Dynamics. Recording the same

Table 1. The 4D-SID domains

Domain	Core variables	Clinical implication
Disease substrate	Malignancy; prior therapies and HCT; baseline immune status and infections; comorbidity and organ reserve[1-5]	Defines pre-existing vulnerability and competing causes of immune dysfunction
Drug and target	Modality/target; lymphodepletion/bridging; combinations; dose/interval; treatment-delivery pattern; toxicity-directed immunosuppression[1–4,6–10,16]	Defines mechanism, intensity, and persistence of treatment-related immune perturbation
Deficit profile	Neutropenia/myeloid abnormalities; humoral or cellular dysfunction; combined deficits; mucosal/epithelial barrier injury[1–4,11–16]	Identifies predominant and overlapping susceptible components of host defense
Dynamics	Time since infusion/start; duration and cumulative exposure; infection events; interruptions/restarts; immune recovery[1–5,11–16]	Determines when reassessment and prevention may need intensification, continuation, adaptation, or de-escalation

Notes: This is an author-derived conceptual organization based on the literature synthesis; it is not a consensus-derived or validated model.
Abbreviation: HCT: Hematopoietic cell transplantation.

clinical event across more than one domain when it has distinct mechanistic and temporal implications is therefore deliberate. In relation to existing approaches, treatment-specific guidance provides prescriptive recommendations within defined settings[1–4,16], while CAR-HEMATOTOX is a weighted baseline risk tool developed for hematotoxicity and infection-related outcomes in CD19-directed CAR T-cell therapy for large B-cell lymphoma.[23,24] By contrast, 4D-SID is unweighted, cross-setting, and designed for repeated state characterization; it is intended to complement rather than replace either guidance or validated setting-specific risk tools.

5. CAR T-cell therapy: time-dependent immunodeficiency

In recipients of CAR T-cell therapy, the timing and spectrum of infections reflect the combined effects of lymphodepletion, acute treatment-related toxicities and their management, treatment-emergent cytopenias, subsequent hematopoietic recovery, and the slower reconstitution of humoral and cellular immunity. Observational evidence and American Society for Transplantation and Cellular Therapy (ASTCT) best-practice considerations indicate that the burden of infection is greatest during the first approximately 100 days after infusion, with bacterial infections predominating during the early neutropenic phase and respiratory viral infections becoming relatively more prominent at later time points.[1,11] Baseline infectious and immunologic assessment, phase-adapted antimicrobial prophylaxis, and vaccination planning should therefore be linked to longitudinal evaluation of hematopoietic and immune recovery.

CD19-directed CAR T-cell therapy can result in prolonged B-cell aplasia and hypogammaglobulinemia. In a retrospective analysis of 579 recipients, hypogammaglobulinemia, defined as IgG ≤600 mg/dL, was documented in 60% before therapy and in approximately 91% after therapy among patients with available IgG measurements; post-treatment hypogammaglobulinemia was associated with an increased rate of serious infection.[5] These findings underscore the importance of characterizing baseline humoral immunity and its subsequent trajectory rather than attributing antibody deficiency solely to CAR T-cell infusion.

BCMA-directed CAR T-cell therapy can deplete normal plasma cells and may result in marked and sometimes prolonged impairment of humoral immunity. Infection risk reflects the interaction of the underlying myeloma, cumulative prior therapy, transplantation history, lymphodepletion, treatment-emergent cytopenias, and the depth and duration of plasma-cell and immunoglobulin depletion. Infectious morbidity may therefore extend beyond the early post-infusion period, particularly when cytopenias or humoral immune deficits persist.[1,3,6–7,17,18]

6. T-cell-engaging bispecific antibodies: sustained exposure and cumulative infection burden

Repeated dosing of T-cell-engaging bispecific antibodies creates an exposure pattern distinct from the single-infusion administration of CAR T-cell products. In multiple myeloma, clinical trials, pooled analyses, systematic reviews, and real-world cohorts consistently document a substantial burden of infection, including grade ≥3 events, particularly during BCMA-directed therapy.[8,10,12–18] During ongoing BCMA-directed treatment, hypogammaglobulinemia may deepen and persist, and

infection rates may remain elevated, resulting in an increasing cumulative burden with longer treatment exposure.[8,10,12–14,16,19] A cumulative infection burden has also been documented with CD20×CD3 bispecific antibodies in B-cell lymphoma. A systematic review and meta-analysis found higher all-grade and grade ≥3 infection rates per patient-month with bispecific antibodies than with CAR T-cell therapy, although corresponding per-patient rates did not differ significantly; a subsequent longitudinal cohort found that cumulative incidence continued to rise over 24 months.[25,26] These findings support explicit consideration of treatment duration and time at risk but should not be extrapolated directly across disease settings because target biology, treatment schedules, prior therapies, populations, and follow-up differ. Figure 2 therefore depicts only qualitative time-specific infection vulnerability in separate, non-comparable panels for CAR T-cell and repeated or continuous T-cell-engaging antibody therapy; cumulative infection burden is not plotted and should not be inferred from the trajectory of time-specific vulnerability.

In a retrospective single-center cohort of 80 patients treated with teclistamab, longer dosing intervals were associated with lower annualized rates of both all-grade and severe infections.[13] Because interval extension is generally response-adapted and occurs in selected patients who remain on therapy, these findings should not be interpreted as evidence of a causal protective effect without prospective studies or rigorously designed analyses accounting for time-varying treatment exposure and selection. BCMA-directed bispecific antibodies, including teclistamab and elranatamab, can cause marked hypogammaglobulinemia and sustained impairment of polyclonal humoral immunity.[8,10,12,16] Reported infectious complications include bacterial and respiratory viral infections; viral reactivations, PJP, invasive fungal disease, and other opportunistic infections have also been described, particularly in patients with additional or overlapping risk factors.[2–3,8,10,12–20] GPRC5D-directed talquetamab has a distinct on-target toxicity profile, including dysgeusia, xerostomia, and other oral or epithelial effects.[9,21] Infections nevertheless remain clinically relevant during talquetamab therapy. Available evidence does not establish that this risk is attributable to GPRC5D targeting itself; cumulative prior treatment, baseline immune dysfunction, lymphopenia or cytopenias, combination therapy, corticosteroid exposure, and treatment duration are likely important modifiers.[9,14,17,18]

The distinction between BCMA- and GPRC5D-directed therapy is therefore clinically relevant but not deterministic. Target-related effects interact with baseline immune reserve, previous infections, prior and concomitant therapies, corticosteroid exposure, cytopenia, treatment duration and dosing interval, and immunoglobulin replacement. The 4D-SID framework is intended to preserve these interactions and their temporal evolution rather than assign a fixed infection-risk category on the basis of target or therapeutic class alone. Therapy-specific patterns and their supporting evidence are summarized in Table 2.

Table 2. Therapy-specific patterns of secondary immunodeficiency

Therapy context	Characteristic immune effects	Typical infection pattern / concern
CD19 CAR T	B-cell aplasia; hypogammaglobulinemia; early cytopenia; delayed CD4-positive T-cell recovery	Early bacterial infections; later respiratory viral/bacterial infections; opportunistic events in selected patients with persistent or combined deficits[1,5,11]
BCMA CAR T	Plasma-cell depletion; hypogammaglobulinemia; cytopenia; heavily pretreated myeloma substrate	Respiratory bacterial/viral burden may extend beyond the early phase when cytopenia or humoral deficits persist[1,3,6–7,17,18]
BCMA bispecific antibody	Repeated or continuous plasma-cell suppression; marked hypogammaglobulinemia; other immune dysfunction; treatment-related cytopenia	Infection rates may remain elevated and cumulative burden may increase; viral reactivation and opportunistic infection in higher-risk patients[2–4,8,10,12–20]
GPRC5D bispecific antibody	Distinct target biology; oral/epithelial on-target effects; background immune dysfunction from myeloma and prior treatment	Clinically relevant infections occur; phenotype modified by prior treatment, cytopenia, combinations, and treatment duration[9,14,17,18,21]
CD20/CD19 T-cell engagers	B-cell depletion with T-cell engagement; variable cytopenia and corticosteroid exposure	Bacterial/viral burden shaped by prior therapy and treatment duration; opportunistic events in selected higher-risk patients[25,26]

Notes: Table 2 is an author-derived descriptive synthesis, not a guideline algorithm.
Abbreviations: BCMA: B-cell maturation antigen; CAR T: chimeric antigen receptor T cell; GPRC5D: G protein-coupled receptor class C group 5 member D.

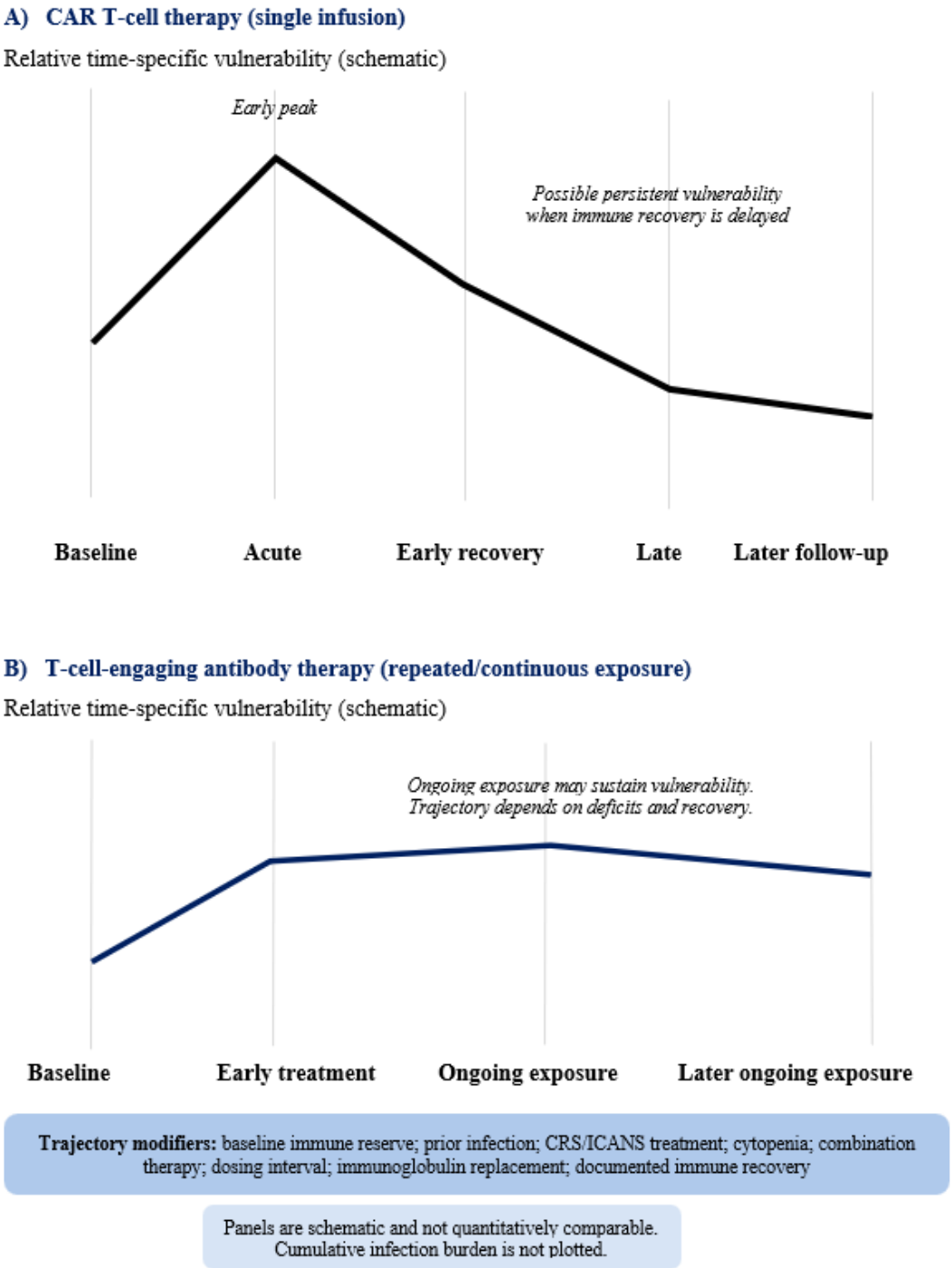


Figure 2. Conceptual time-specific infection vulnerability after immune-effector therapy. Panel A illustrates a qualitative early peak in time-specific vulnerability after CAR T-cell therapy followed by variable decline and possible persistent late vulnerability when immune recovery is delayed. Panel B illustrates qualitative time-specific vulnerability during repeated or continuous T-cell-engaging antibody exposure. The panels are schematic, use separate non-quantitative scales, and are not intended to rank or compare modalities. Cumulative incidence or cumulative infection burden is not plotted and may increase as events accrue even when time-specific vulnerability is stable or declining. Trajectories are modified by baseline immune reserve, infection history, toxicity-directed immunosuppression, cytopenias, combination therapy, dosing interval, immunoglobulin replacement, and documented immune recovery.

Abbreviations: CAR T: Chimeric antigen receptor T cell; CRS: Cytokine release syndrome; ICANS: Immune effector cell-associated neurotoxicity syndrome.

7. From laboratory abnormalities to clinically meaningful deficit profiles

Quantitative serum immunoglobulin measurements, particularly IgG, are clinically informative but do not fully characterize humoral immune competence. In plasma-cell disorders, total IgG may be difficult to interpret because a monoclonal component can contribute to the measured concentration, while recent immunoglobulin replacement can transiently raise total IgG and may also influence measured pathogen- or vaccine-specific antibody titers. Apparent laboratory improvement therefore does not, by itself, establish endogenous humoral recovery. Where relevant and available, interpretation should integrate the monoclonal-protein burden or uninvolved/polyclonal immunoglobulin component, the timing and dose of recent IgRT, infection trajectory, recovery of B-cell or plasma-cell compartments, vaccination history, and antigen-specific antibody responses when these results are clinically actionable.[1–2,12,16] Functional antibody testing may add information but is not uniformly available or validated for all treatment settings, and a single total-IgG threshold should not be treated as a universal definition of recovery. Similarly, the absolute lymphocyte count is an imprecise surrogate for cellular immunity and does not directly establish CD4-positive T-cell number or function. The 4D-SID framework therefore interprets laboratory abnormalities in their clinical and temporal context and distinguishes isolated measurements from the broader immune-deficit phenotype most relevant to infection susceptibility.

Within the framework, a predominantly myeloid phenotype is characterized primarily by severe or prolonged neutropenia and is most relevant to bacterial infection during neutropenic periods. Susceptibility to invasive fungal disease becomes more important when neutropenia is profound or prolonged or when additional risk factors coexist. A predominantly humoral phenotype may be indicated by B-cell aplasia, plasma-cell depletion, immunoparesis, reduced polyclonal immunoglobulins, or impaired antigen-specific antibody responses; recurrent predominantly sinopulmonary infections may provide corroborating clinical evidence. A predominantly cellular phenotype is suggested by persistent T-cell lymphopenia, low CD4-positive T-cell counts, or other evidence of impaired T-cell immunity and may increase susceptibility to viral reactivation and selected opportunistic infections. These phenotypes are not mutually exclusive: combined deficits are common and may evolve over time.[1-4,11] Mucosal or epithelial barrier injury is included as a potential modifying domain because disruption of local host defenses may alter local susceptibility and pathogen-entry pathways. For target-related oral toxicities, however, an independent contribution to systemic infection risk has not been established.[9,21]

8. Monitoring and prevention

Baseline assessment should characterize both pre-existing and treatment-related susceptibility to infection. It should include a history of severe or recurrent infections; prior and current antimicrobial exposure; vaccination history; a complete blood count with differential; quantitative IgG, IgA, and IgM; and lymphocyte subsets when the results are expected to influence management. Screening for latent or chronic viral infections should follow product labeling, institutional protocols, and society guidance; hepatitis B virus (HBV) screening is particularly important before therapies associated with profound B-cell depletion or other substantial immunosuppression. Clinically significant active infections should be identified and treated or adequately controlled before lymphodepletion or initiation of immune-effector therapy whenever feasible.[1-4] A proposed core longitudinal monitoring dataset is summarized in Table 3.

Antimicrobial prophylaxis should be adapted to the treatment setting and phase, applicable therapy-specific recommendations, the evolving immune-deficit profile, and additional patient-specific risk factors. Phenotype classification is an organizing layer and does not remove prophylaxis recommended for a treatment population as a whole (Table 4). Herpes simplex virus (HSV)/varicella-zoster virus (VZV) prophylaxis and *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis are broadly recommended after CAR T-cell therapy and during T-cell-engaging bispecific-antibody treatment, including myeloma bispecific-antibody therapy without requiring prior demonstration of a cellular-deficiency phenotype.[1–4,11,16] Antibacterial recommendations are less uniform. ASTCT best-practice considerations and the COMMIT recommendations emphasize prophylaxis during severe neutropenia after CAR T-cell therapy.[1,3] For myeloma bispecific antibodies, Mohan *et al.*[3] recommend antibacterial prophylaxis from treatment onset through the first month and resumption when the absolute neutrophil count is <500/μL, whereas Raje *et al.*[2] do not recommend routine prophylaxis for all recipients but support it for prolonged neutropenia, selected high-risk patients, and those with recurrent bacterial infections, with discontinuation when the risk is lower and neutropenia has resolved. These distinctions argue against presenting severe neutropenia as the single universally agreed indication. Routine systemic antifungal prophylaxis is likewise not indicated for all recipients; when warranted, agent selection and duration should reflect the anticipated

Table 3. Proposed core longitudinal monitoring dataset

Time point / trigger	Core assessment
Baseline	Infection and vaccination history; CBC/differential; IgG/IgA/IgM; renal/hepatic function; HBV/HCV/HIV screening per guidance; disease and prior-treatment history.[1-4]
Early high-risk phase	CBC/differential; febrile or infectious symptoms; antimicrobial exposure; CRS/ICANS treatment; cultures and imaging as clinically indicated.[1,3,11]
Ongoing during prolonged bispecific-antibody therapy	CBC and quantitative immunoglobulins at intervals guided by product, treatment phase, and risk; infections and antimicrobial use; treatment dose/interval; IgRT; lymphocyte subsets when actionable.[2–4,16]
Routine later follow-up after CAR T-cell therapy (especially with persistent deficits)	CBC/differential; quantitative immunoglobulins; interval infection and antimicrobial history; IgRT exposure; vaccination status; B-cell and/or CD4-positive T-cell recovery when clinically relevant. Continue reassessment even in the absence of a new infection or documented recovery.[1,11]
After severe/recurrent infection	Microbiologic diagnosis where feasible; immune reassessment; prophylaxis and IgRT review; treatment intensity and dosing-interval review. [1–4,11,16]
At evidence of immune recovery	Reassess need for prophylaxis; vaccination/revaccination; document B-cell and CD4-positive T-cell recovery when relevant. Interpret apparent humoral recovery in the context of monoclonal-protein contribution and recent IgRT; consider functional antibody responses when clinically actionable.[1–2,12,16]

Notes: This is a proposed author-derived core dataset, not an established minimum standard. Monitoring frequency and tests should follow product-specific labeling, applicable guidance, treatment phase, clinical events, and local protocols.
Abbreviations: CBC: Complete blood count; CD4: Cluster of differentiation 4; CRS: Cytokine release syndrome; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; ICANS: Immune effector cell-associated neurotoxicity syndrome; IgA/IgG/IgM: Immunoglobulin A/G/M; IgRT: Immunoglobulin replacement therapy.

Table 4. Prevention mapped to immune deficit

Dominant deficit	Potential preventive focus	Important caveat
Severe neutropenia	Rapid fever evaluation; institution-specific antibacterial strategy; risk-adapted antifungal prophylaxis.[1–4,11,16]	Reassess prophylaxis when neutropenia resolves.
Humoral deficiency	Vaccination; early respiratory-pathogen testing; consider IgRT according to immune phenotype, infection history, and applicable guidance.[1–4,12,16]	Total IgG alone does not fully characterize functional humoral immunity; interpret alongside monoclonal-protein contribution, timing of recent IgRT, infection trajectory, and functional antibody data when available.
Cellular deficiency	PJP prophylaxis; antiviral prophylaxis; assess opportunistic-pathogen risk with corticosteroids or prolonged lymphopenia.[1–4,11,16]	Duration should reflect treatment context and documented immune recovery.
Combined deficit	Layered prophylaxis and a lower threshold for infectious-disease consultation.[1–4,11,16]	Drug interactions, toxicity, resistance, and treatment burden must be balanced.
Barrier injury	Oral/skin care; prompt assessment of mucosal lesions or infection; nutrition and supportive care.[9,21]	Its direct contribution to systemic infection risk may be difficult to isolate.

Notes: The deficit categories are an organizing device and do not supersede prophylaxis recommended for a treatment population as a whole. In particular, broad PJP and HSV/VZV prophylaxis during myeloma bispecific-antibody therapy should not require documented cellular deficiency.[2-4,16]
Abbreviations: HSV: Herpes simplex virus; IgRT: Immunoglobulin replacement therapy; PJP: *Pneumocystis jirovecii* pneumonia; VZV: Varicella-zoster virus.

pathogen spectrum, prolonged or profound neutropenia, substantial corticosteroid exposure, previous invasive mold disease, other recognized high-risk features, drug interactions, toxicity, local epidemiology, antimicrobial resistance, and stewardship considerations.[1–4,11,16]

Immunoglobulin replacement therapy (IgRT) remains an area of evolving practice, and recommendations differ by treatment setting. Some guidance favors selective, phenotype-guided replacement in patients with marked hypogammaglobulinemia, particularly when accompanied by recurrent or severe infections, whereas myeloma-specific consensus recommendations may support more proactive replacement during bispecific-antibody therapy.[1-4,16] The relevant differences in thresholds, clinical triggers, and

duration are preserved in Table 5 rather than harmonized into a single rule. Retrospective studies of BCMA-directed bispecific antibodies have associated intravenous immunoglobulin (IVIG) exposure with substantially lower rates of serious infection.[12,19] In a multicenter retrospective cohort of 225 patients, initiation of IVIG before the first documented infection was associated with longer infection-free survival after adjustment for immortal-time bias; however, the 12-month cumulative incidences of all-grade and grade ≥3 infections did not differ significantly between groups.[20] A 2026 single-center teclistamab cohort likewise associated IVIG exposure with lower annualized rates of both all-grade and severe infections.[13] These findings are clinically important but remain observational. Residual confounding, treatment-selection bias, heterogeneous initiation criteria, and variable replacement schedules limit causal inference and do not establish a universal IgG threshold or optimal dosing strategy. Prospective or rigorously designed comparative-effectiveness studies therefore remain a priority.

Vaccination should be integrated into longitudinal care before and after CAR T-cell therapy and during prolonged bispecific-antibody treatment in accordance with current treatment-specific recommendations (Table 5). Timing should account for time since infusion or treatment initiation, ongoing therapy and immunosuppression, documented immune reconstitution, and recent IgRT where relevant. Vaccine responses may be attenuated during active B-cell or plasma-cell depletion[1–4,12], but vaccination should not be omitted solely because reduced immunogenicity is anticipated. Live-attenuated vaccines should generally be avoided unless their use is specifically permitted by applicable guidance after adequate immune recovery. Vaccination of close contacts in accordance with current recommendations, prompt diagnostic testing when infection is suspected, and early pathogen-directed treatment when indicated provide complementary layers of protection.

9. A phenotype-guided care pathway

Figure 3 operationalizes the 4D-SID framework through five iterative steps: characterize, measure, classify, match prevention, and reassess. This pathway is intended to complement—not replace—product-specific labeling, institutional protocols, and guideline-based recommendations. The 'match prevention' step concerns supportive-care measures. Any interruption, dose or interval change, de-escalation, or other modification of anticancer treatment remains a decision of the treating team and should follow applicable product-specific guidance; the 4D-SID framework has not established the safety or efficacy of anticancer-treatment de-escalation. Monitoring frequency and preventive intensity should be informed by both the treatment context and the predominant, evolving immune-deficit profile rather than by the therapy name alone. For example, a patient with grade 4 neutropenia early after CAR T-cell infusion would generally require neutropenia-directed monitoring and preventive measures, whereas a patient one year later with neutrophil recovery but persistent B-cell aplasia and recurrent bacterial respiratory infections would warrant greater emphasis on humoral immune assessment and phenotype-appropriate prevention. Similarly, a patient with a deep or sustained response during prolonged BCMA-directed bispecific-antibody therapy may remain vulnerable to infection if substantial humoral immune impairment persists.[1-4]

Reassessment should occur at prespecified intervals and whenever clinically meaningful events alter the immune state or treatment exposure. Relevant triggers include a grade ≥3 infection or recurrent infections; treatment interruption or restart; a clinically meaningful change in dosing interval; new or intensified corticosteroid or other immunosuppressive exposure; prolonged or biphasic cytopenias; initiation of immunoglobulin replacement; documented B-cell or CD4-positive T-cell recovery; and a major change in disease status. Each trigger should prompt reconsideration of the current deficit profile and, where appropriate, adjustment of monitoring, antimicrobial prophylaxis, vaccination planning, immunoglobulin replacement, or other risk-adapted supportive-care measures. This event-informed approach provides a practical structure for longitudinal supportive care and may support future digital monitoring and clinical decision-support models, although its clinical utility requires prospective evaluation.

Digitally enabled monitoring could extend this event-informed pathway beyond the treatment center by integrating patient-reported symptoms, laboratory trajectories, treatment exposure, clinically significant events, and the current 4D-SID state within a patient-facing digital companion. Existing work has established baseline risk-stratification approaches[23,24], defined candidate electronic patient-reported outcome domains and patient- and caregiver-reported warning signs[27-29], and demonstrated the feasibility of technology-assisted home monitoring in a small prospective study.[30] These data do not establish that a patient-facing infection-risk score improves infection-related outcomes or can safely prescribe or relax protective behaviors. Once an underlying dynamic model and its decision thresholds have been adequately developed and validated, such a system could provide version-controlled, clinician-approved updates

Table 5. Selected treatment-specific guidance for infection monitoring and prevention

Domain	CAR T-cell therapy	T-cell-engaging bispecific-antibody therapy in multiple myeloma
Monitoring / reassessment	Baseline infectious and immune assessment and phase-adapted early monitoring are recommended. ASTCT supports serum IgG measurement before and during the first 3 months after CAR T-cell therapy; later frequency is individualized according to persistent cytopenia, humoral/cellular deficits, infections, and immune recovery. No single fixed long-term interval is established.[1,11]	Baseline infection/immune assessment and ongoing clinical, CBC, and quantitative-immunoglobulin surveillance are recommended during therapy. Raje *et al.* specify monthly Ig monitoring during Ig replacement; a universal interval for all laboratory monitoring is not established across guidance.[2–4,16]
Antibacterial prophylaxis	ASTCT/COMMIT approaches emphasize prophylaxis during severe neutropenia (*e.g.*, ANC <500/μL) until neutrophil recovery; institutional practice and local resistance patterns remain relevant.[1,3]	Not uniform across consensus sources: COMMIT recommends prophylaxis from treatment onset through the first month and again when ANC <500/μL; Raje *et al.* advise against routine prophylaxis for all patients but support it for prolonged neutropenia, selected high-risk patients, or recurrent bacterial infection, stopping when risk/neutropenia resolves.[2,3]
HSV/VZV prophylaxis	Start with lymphodepletion and continue for at least 6 months in ASTCT best-practice considerations; longer duration may be appropriate with persistent immunosuppression or delayed immune recovery.[1,11]	Broad prophylaxis during bispecific-antibody therapy is recommended by myeloma consensus statements; exact post-treatment stopping criteria are not uniform across sources.[2–4,16]
PJP prophylaxis	Initiate after count recovery/by approximately day 30 and continue for at least 6 months; some guidance additionally uses CD4 >200/μL as a stopping criterion.[1,3,11]	Broad prophylaxis from treatment onset and during therapy is recommended. COMMIT continues prophylaxis for the duration of therapy or until CD4 >200/μL, whichever is longer; exact post-treatment criteria are not uniform.[2–4,16]
Antifungal prophylaxis	Not universal for all recipients. Neutropenia-directed prophylaxis is used, with mold-active coverage considered for prolonged/profound neutropenia, substantial corticosteroid exposure, previous invasive mold disease, or other high-risk features.[1,3,11]	Routine systemic prophylaxis is not recommended for all recipients; consider it in prolonged/profound neutropenia or other recognized high-risk states, with agent selection guided by anticipated pathogens and local practice.[2–4,16]
Vaccination timing	Influenza and SARS-CoV-2 vaccination may begin from approximately 3 months after CAR T-cell therapy when clinically appropriate; other inactivated vaccines are generally restarted from approximately 6 months, with timing adapted to immune recovery, ongoing immunosuppression, vaccine type, and recent IgRT.[1,3]	Update indicated vaccines before treatment when feasible and continue non-live vaccination according to applicable schedules. Optimal timing and expected immunogenicity during continuous B-cell/plasma-cell-directed therapy are not defined by a single uniform schedule.[2–4,16]
IgRT indications / duration	ASTCT supports selective replacement, particularly for IgG ≤400 mg/dL with severe or recurrent bacterial infection; COMMIT (multiple myeloma) proposes a more proactive strategy from day +30 through 1 year and thereafter until IgG >400 mg/dL. Scope is therefore not uniform.[1,3]	Raje *et al.* consider IgRT for IgG <400 mg/dL, recurrent severe encapsulated-bacterial infections regardless of IgG, life-threatening infection, or inadequate response to antibiotics, with monthly treatment during immunoparesis until IgG ≥400 mg/dL. COMMIT proposes replacement from month 2 through therapy or until IgG >400 mg/dL.[2,3]

Sources: Treatment-specific guidance and consensus statements.[1–4,16] Entries summarize selected recommendations without replacing product labeling, full guidance documents, institutional protocols, or individualized clinical assessment. 'Not uniform' indicates that the cited guidance differs or does not provide a single established criterion. Recommendations are largely consensus/best-practice based rather than supported by randomized comparative trials.

Abbreviations: ANC: absolute neutrophil count; ASTCT: American Society for Transplantation and Cellular Therapy; CAR T: Chimeric antigen receptor T cell; CBC: Complete blood count; COMMIT: Academic Consortium to Overcome Multiple Myeloma through Innovative Trials; HSV: Herpes simplex virus; IgG: Immunoglobulin G; IgRT: Immunoglobulin replacement therapy; PJP: *Pneumocystis jirovecii* pneumonia; VZV: Varicella-zoster virus.

reflecting emerging evidence, changes in vaccination or prophylaxis guidance, and relevant seasonal or outbreak-related pathogen circulation. It could translate these inputs into time-limited, guideline-concordant action tiers—for example, prompt diagnostic testing, rapid contact with the treatment center, vaccination or prophylaxis review, or enhanced protection in high-exposure settings—while preserving clinician oversight. Low-risk classifications must not create false reassurance, and high-risk classifications should not trigger disproportionate social restriction without demonstrated net clinical benefit.

10. Research priorities

Priority should be given to prospective, preferably multicenter infection surveillance using standardized case definitions, ascertainment procedures, and a consensus-

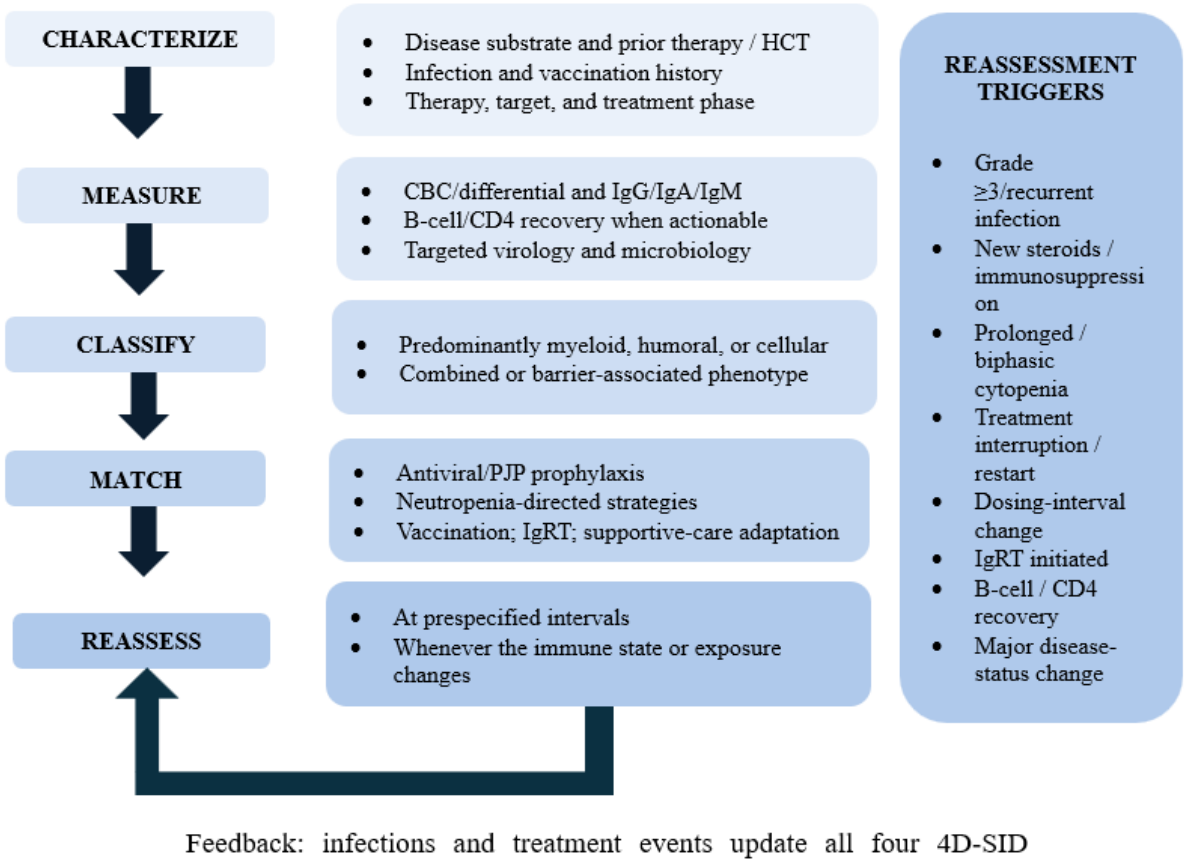


Figure 3. Phenotype-guided supportive-care pathway. Iterative characterization, measurement, phenotype classification, matching of prevention, and reassessment are shown. 'Supportive-care adaptation' refers to monitoring, prophylaxis, vaccination, IgRT, and related supportive measures. Anticancer-treatment modification remains subject to treating-team assessment and applicable product-specific guidance; 4D-SID does not establish the safety or efficacy of treatment de-escalation.

Abbreviations: CBC: Complete blood count; CD4: Cluster of differentiation 4; HCT: Hematopoietic cell transplantation; Ig: Immunoglobulin; IgRT: Immunoglobulin replacement therapy; PJP: *Pneumocystis jirovecii* pneumonia.

based core outcome set. Studies should capture the timing, site, severity, microbiologic confirmation, and recurrence of infections; antimicrobial exposure; longitudinal immunoglobulin concentrations and lymphocyte-subset trajectories; vaccination and, where feasible, vaccine responses; the indication, timing, and duration of IgRT; corticosteroid and other immunosuppressive exposures; treatment intensity, dosing interval, interruption, and discontinuation; and patient-reported burden. Time-to-first-event outcomes, including infection-free survival, should be complemented by the cumulative incidence of severe infection, recurrent-event rates, infection-related hospitalization and antimicrobial days, treatment interruptions, quality of life, healthcare utilization, and infection-attributable mortality where this can be reliably adjudicated. The handling of death, disease progression, and treatment discontinuation should be linked explicitly to the outcome and estimand. Death before a first infection precludes that event and is therefore a competing event for a time-to-first-infection endpoint. By contrast, disease progression and treatment discontinuation do not necessarily prevent subsequent infection; depending on the research question they may be handled as intercurrent events, time-varying exposures, censoring events only under justified assumptions, or competing events for outcomes that they truly preclude. This distinction is particularly important when immune deficits persist after treatment discontinuation. Analyses should therefore prespecify the estimand, event-handling strategy, and relevant time-varying treatment and supportive-care exposures. Recent systematic reviews and meta-analyses underscore both the substantial burden of infectious

morbidity and the limitations of indirect comparisons across therapeutic modalities, targets, and disease settings.[17,18,25–26]

Dynamic prediction models should be developed within clearly defined disease–therapy contexts using prespecified candidate predictors derived from the 4D-SID domains and repeated measurements where available. Model development should include rigorous internal validation and assessment of discrimination, calibration, and potential clinical utility, followed by external validation in independent centers and patient populations. The 4D-SID framework identifies candidate domains for longitudinal risk characterization but is not itself a weighted or validated prediction model. Existing scores such as CAR-HEMATOTOX may inform candidate variables and study design but should not be assumed to generalize across targets, diseases, time points, or patient-facing applications.[23,24] After adequate validation, prospective impact studies should determine whether model-informed monitoring and prevention improve patient-important outcomes while limiting avoidable antimicrobial exposure, IgRT use, toxicity, treatment burden, and resource use. Digital implementations should additionally be evaluated for robustness to missing data, calibration drift, equity, alert burden, privacy, cybersecurity, usability, and potential harms from false reassurance or unnecessary restriction. Patient-facing outputs should be co-designed with patients and caregivers, linked to clinician-approved, guideline-concordant actions, and supported by transparent, version-controlled content governance for updates to evidence, vaccination or prophylaxis recommendations, and relevant seasonal or outbreak-related pathogen information rather than by unsupervised behavioral prescriptions.[27-30]

Randomized trials and prospective pragmatic studies are particularly needed to define the indications, thresholds, timing, dosing, and duration of IgRT; the effects of response-adapted extension of bispecific-antibody dosing intervals; and the optimal initiation and discontinuation of PJP and antiviral prophylaxis in specific risk groups.[13,19,20] Where randomization is not feasible, rigorously designed comparative-effectiveness studies or target-trial emulations should explicitly address treatment-selection bias, immortal-time bias, time-varying confounding, and competing risks. Future studies should assess functional humoral immunity—including pathogen- or vaccine-specific antibody responses—and pathogen-specific cellular immunity rather than relying on total IgG alone. Standardized definitions of immune recovery are also needed to determine whether functional and longitudinal immune measures improve risk prediction beyond routinely available laboratory variables.

11. Conclusions

Secondary immunodeficiency after CAR T-cell and T-cell-engaging antibody therapy is best understood not as a single treatment toxicity or as a synonym for hypogammaglobulinemia, but as a heterogeneous and evolving clinical state. Its expression reflects interactions among the underlying disease and prior treatment, the immune-effector modality and therapeutic target, the predominant—and often overlapping—immune-deficit profile, and changes in treatment exposure and immune recovery over time. The 4D-SID framework provides a pragmatic structure for characterizing this complexity longitudinally and for relating monitoring and preventive strategies to the treatment phase and evolving immune phenotype. It is a descriptive framework rather than a weighted or validated prediction model, and its clinical utility and implementation require prospective evaluation. As immune-effector therapies are introduced earlier in the disease course and, for some agents, administered over prolonged periods, longitudinal phenotype-guided reassessment may help refine prevention where duration or intensity is conditional or uncertain. Guideline- or product-directed prophylaxis that applies to a treatment population should remain in place where recommended; phenotype-guided reassessment is intended to complement, not replace, those measures.

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Appendix

Supplementary methods: Reproducible literature-search for the 4D-SID review

Review design

This state-of-the-art review was designed as an integrative and conceptual synthesis rather than as a systematic review or quantitative evidence synthesis. Structured PubMed/MEDLINE searches were combined with reference-list screening of relevant society guidance, consensus statements, systematic reviews and meta-analyses, pivotal clinical trials, and recent real-world cohorts. No protocol was registered, and no formal dual-reviewer screening, risk-of-bias assessment, certainty-of-evidence grading, or meta-analysis was undertaken.

Framework development and domain derivation

The four 4D-SID domains were selected by the author through iterative conceptual grouping of recurrent constructs identified across the included guidance and consensus documents, infection and immune-reconstitution studies, treatment-specific cohorts, and relevant risk-stratification literature. The domains were refined to separate relatively pre-existing vulnerability (Disease substrate), current therapeutic mechanism and exposure (Drug and target), the observed immune-deficit phenotype (Deficit profile), and longitudinal change in exposure or immune state (Dynamics). This was an author-derived conceptual organization; no Delphi process, formal consensus exercise, data-driven feature-selection procedure, weighting step, or clinical validation study was performed. Domain overlap is deliberate: for example, current dose and dosing interval are recorded under Drug and target, whereas cumulative exposure, interval changes, treatment interruption/restart, and recovery over time are recorded under Dynamics.

Database, search date, and scope

PubMed/MEDLINE was searched from database inception through 26 August 2026. No publication-date restriction was applied. Peer-reviewed human clinical evidence in hematologic malignancies was prioritized. The search focused on infection epidemiology, secondary immunodeficiency, immune reconstitution, monitoring, vaccination, antimicrobial prophylaxis, immunoglobulin replacement therapy, treatment-exposure patterns, infection-risk stratification, digitally enabled home monitoring, and patient-facing clinical decision support after CAR T-cell or T-cell-engaging antibody therapy.

Search strategy

The following search blocks document the concepts used for the final update. Syntax may be adapted to future PubMed indexing changes. Asterisks indicate truncation. Searches were supplemented by narrower combinations of individual products, targets, pathogens, and supportive-care interventions when required to verify specific statements.

Search A: CAR T-cell therapy and infection or immune dysfunction

(("Receptors, Chimeric Antigen"[Mesh] OR "chimeric antigen receptor T cell*"[Title/Abstract] OR "CAR T cell*"[Title/Abstract] OR CAR-T[Title/Abstract]) AND ("Infections"[Mesh] OR infection*[Title/Abstract] OR immunodeficien*[Title/Abstract] OR hypogammaglobulin*[Title/Abstract] OR "immune reconstitution"[Title/Abstract] OR cytopenia*[Title/Abstract] OR prophylaxis[Title/Abstract] OR vaccination[Title/Abstract] OR immunoglobulin*[Title/Abstract]))

Search B: T-cell-engaging bispecific antibodies and infection or immune dysfunction

(("Antibodies, Bispecific"[Mesh] OR "bispecific antibod*"[Title/Abstract] OR "T-cell engager*"[Title/Abstract] OR "T-cell-engaging"[Title/Abstract] OR BiTE[Title/Abstract]) AND (CD19[Title/Abstract] OR CD20[Title/Abstract] OR BCMA[Title/Abstract] OR "B-cell maturation antigen"[Title/Abstract] OR GPRC5D[Title/Abstract] OR "multiple myeloma"[Title/Abstract] OR lymphoma*[Title/Abstract]) AND (infection*[Title/Abstract] OR immunodeficien*[Title/Abstract] OR hypogammaglobulin*[Title/Abstract] OR "immune reconstitution"[Title/Abstract] OR cytopenia*[Title/Abstract] OR prophylaxis[Title/Abstract] OR vaccination[Title/Abstract] OR immunoglobulin*[Title/Abstract]))

Search C: Monitoring and preventive interventions

(("CAR T"[Title/Abstract] OR CAR-T[Title/Abstract] OR "bispecific antibod*"[Title/Abstract] OR "T-cell engager*"[Title/Abstract]) AND (prophylaxis[Title/Abstract] OR antiviral*[Title/Abstract] OR antibacterial*[Title/Abstract] OR antifungal*[Title/Abstract] OR Pneumocystis[Title/Abstract] OR PJP[Title/Abstract] OR vaccination[Title/Abstract] OR

"immunoglobulin replacement"[Title/Abstract] OR IVIG[Title/Abstract] OR IgRT[Title/Abstract])))

Search D: Risk stratification and digitally enabled monitoring

(("CAR T"[Title/Abstract] OR CAR-T[Title/Abstract] OR "bispecific antibod*"[Title/Abstract] OR "T-cell engager*"[Title/Abstract]) AND ("risk score"[Title/Abstract] OR "prediction model"[Title/Abstract] OR "risk stratification"[Title/Abstract] OR "CAR-HEMATOTOX"[Title/Abstract] OR "digital monitoring"[Title/Abstract] OR "remote monitoring"[Title/Abstract] OR "remote patient monitoring"[Title/Abstract] OR "home monitoring"[Title/Abstract] OR wearable*[Title/Abstract] OR "digital health"[Title/Abstract] OR "mobile application*"[Title/Abstract] OR chatbot*[Title/Abstract] OR "clinical decision support"[Title/Abstract] OR "electronic patient-reported outcome"[Title/Abstract] OR ePRO[Title/Abstract] OR "patient-reported"[Title/Abstract] OR "caregiver-reported"[Title/Abstract]))

Evidence selection and prioritization

Priority was given to: (1) society guidance and consensus recommendations directly addressing CAR T-cell or bispecific-antibody supportive care; (2) systematic reviews and meta-analyses; (3) pivotal clinical trials reporting infectious or immune outcomes; (4) larger retrospective, multicenter, or real-world cohorts; and (5) studies of immune reconstitution, vaccination, antimicrobial prophylaxis, immunoglobulin replacement, treatment-interval modification, risk stratification, electronic patient-reported outcomes, or technology-assisted home monitoring. Evidence from multiple myeloma received greater emphasis because the most detailed data on prolonged T-cell-engager-associated immune dysfunction currently derive from BCMA-directed therapy, with more limited but clinically relevant evidence for GPRC5D-directed agents. Evidence from B-cell lymphoma and CD19-directed CAR T-cell therapy was incorporated where relevant.

Preclinical studies, non-peer-reviewed reports, and studies without clinically interpretable infection, immune, monitoring, or prevention outcomes were not prioritized. Small case series or case reports were considered only for contextualizing uncommon opportunistic infections and were not used to derive quantitative estimates. Reference lists of key guidance documents, reviews, and primary studies were screened to identify additional eligible sources.

Extraction of treatment-specific guidance for the revised comparison table

For the revision, the already included treatment-specific guidance and consensus sources for CAR T-cell therapy and multiple-myeloma bispecific-antibody therapy were re-examined to extract the distinctions requested by the reviewers: monitoring frequency where specified, antibacterial/antiviral/PJP/antifungal prophylaxis initiation and discontinuation criteria, vaccination timing, and IgRT indications or duration. The revised comparison table preserves source-specific differences rather than forcing heterogeneous recommendations into a single rule. Where the cited sources did not define a uniform interval or stopping criterion, this is stated explicitly. This focused extraction was performed to clarify the clinical tables; it was not a formal guideline-quality appraisal or recommendation-grading exercise.

Evidence interpretation and wording

Recommendations were attributed to the relevant guideline or consensus source and were not presented as universally evidence-proven interventions. Findings from retrospective or nonrandomized studies were described as associations and were qualified for residual confounding, treatment-selection bias, immortal-time bias, time-varying exposure, and heterogeneous follow-up where applicable. Cross-study comparisons across products, targets, or diseases were interpreted cautiously because patient populations, prior treatment, infection definitions, prophylaxis practices, treatment duration, and time at risk differ. Differences among consensus and best-practice sources were retained when recommendations diverged, and areas without a uniform criterion were labeled explicitly rather than harmonized into an artificial consensus.

The 4D-SID framework is a descriptive state-characterization structure and not a weighted or validated prediction model. Existing risk scores, electronic patient-reported outcome studies, and home-monitoring feasibility work were therefore used to define research opportunities rather than to justify autonomous patient-facing behavioral recommendations. Any future digital score should undergo model development, internal and external validation, prospective impact evaluation, usability and equity assessment, and clinician-governed implementation before it is used to prescribe or relax protective behaviors. A patient-facing digital companion should additionally use transparent, version-controlled content governance for updates to emerging evidence, vaccination or prophylaxis recommendations, and relevant seasonal or outbreak-related pathogen information; such updates should remain clinician-approved and should not substitute for urgent clinical assessment.

Reproducibility note

Because this was a state-of-the-art review, the searches were not intended to generate a PRISMA flow diagram or exhaustive study counts. The search blocks above are provided to make the conceptual retrieval strategy transparent and reproducible, while acknowledging that database indexing and the evidence base will continue to evolve after the final update date.